

Optimizing preoperative antibiotics in patients with β -lactam allergies: A role for pharmacy

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Purpose. Patients with a reported β -lactam allergy (BLA) are often given alternative perioperative antibiotic prophylaxis, increasing risk of surgical site infections (SSIs), acute kidney injury (AKI), and *Clostridioides difficile* infection (CDI). The purpose of this study was to implement and evaluate a pharmacist-led BLA clarification interview service in the preoperative setting.

Methods. A pharmacist performed BLA clarification telephone interviews before elective procedures from November 2018 to March 2019. On the basis of allergy history and a decision algorithm, first-line preoperative antibiotics, alternative antibiotics, or allergy testing referral was recommended. The pharmacist intervention (PI) group was compared to a standard of care (SOC) group who underwent surgery from November 2017 to March 2018.

Results. Eighty-seven patients were included, with 50 (57%) and 37 (43%) in the SOC and PI groups, respectively. The most common surgeries included orthopedic surgery in 41 patients (47%) and neurosurgery in 17 patients (20%). In the PI group, all BLA labels were updated after interview. Twenty-three patients were referred for allergy testing, 12 of the 23 (52%) completed BLA testing, and penicillin allergies were removed for 9 of the 12 patients.

Overall, 28 of the 37 (76%) pharmacy antibiotic recommendations were accepted. Cefazolin use significantly increased from 28% to 65% after the intervention ($P = 0.001$). SSI occurred in 5 (10%) patients in the SOC group and no patients in the PI group ($P = 0.051$). All of these

SSIs were associated with alternative antibiotics. Incidence of AKI and CDI was similar between the groups. No allergic reactions occurred in either group.

Conclusion. Implementation of a pharmacy-driven BLA reconciliation significantly increased β -lactam preoperative use without negative safety outcomes.

Keywords: β -lactam allergy, elective surgical procedures, perioperative care, pharmacists, preoperative care, surgical wound infection

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Penicillin allergies are reported in 10% of the general population; however, 90% to 99% of these patients can safely receive β -lactams.¹ First-line antibiotics for surgical infection prophylaxis include cefazolin or cefoxitin, but patients with a reported β -lactam allergy (BLA) are more likely to receive alternative antibiotics such as vancomycin, clindamycin, or gentamicin.^{2,3} These alternatives increase the risk of *Clostridioides difficile* infection (CDI) and acute kidney injury (AKI) and the potential to develop antibiotic resistance.³ One study demonstrated that patients with reported penicillin allergies had 50% increased odds of developing a surgical site infection (SSI), attributable to receiving alternative antimicrobial prophylaxis.³ SSIs are associated with short- and long-term patient harm such as rehospitalization, prolongment of hospital length of stay (LOS) by 7 to 10 days, and lower quality of life, infection-related complications, a mortality rate of 3%, and an estimated cost of over \$25,000 and penalties in procedure reimbursement.⁴⁻⁶

National guidelines recommend clarifying all BLAs, but many are unclarified before giving alternative antibiotics in the perioperative setting.² Previous studies have described successful allergy interventions such as BLA interviews, cross-reactivity charts, β -lactam skin testing, and oral β -lactam antibiotic challenge in the preoperative setting.⁷⁻¹⁰ These studies showed significant increases in β -lactam antibiotic prophylaxis use and operating room time saved when the prolonged infusion time of vancomycin was avoided.

Pharmacists are well trained and positioned to optimize preoperative antibiotic selection to potentially decrease intraoperative time, adverse effects, and risk of SSI. The purpose of this study was to implement and evaluate a pharmacist-led BLA interview to optimize surgical infection prophylaxis.

Methods

Study design and patient population. This was a single-center, quasi-experimental study at a large academic medical center with about 1,200 elective surgical cases performed monthly. Select patients meeting criteria were seen at our institution's perioperative optimization clinic for clearance about 2 to 3 weeks before surgery. These patients included higher-risk patients such as those who had a recent ST-elevation myocardial infarction or cardiovascular event, patients on home oxygen, patients with end-stage renal disease or end-stage liver disease, and patients who were fully dependent. In addition, patients undergoing high- and intermediate-risk procedures were seen in the perioperative optimization clinic, including patients undergoing aortic, open vascular, or open thoracic surgeries, surgeries expected to last more than 4 hours, surgeries with large fluid shifts anticipated, neurosurgery, or intraabdominal, orthopedic, or ear, nose, and throat surgery. Patients were included if they had a BLA, a perioperative optimization clinic appointment, and a surgery where a β -lactam antibiotic was considered first for SSI prophylaxis.¹¹ Exclusion criteria included non-English speakers, pregnancy, and transplant surgery. The study was approved by the institution's investigational review board with waiver of consent.

Intervention. Before implementation, pharmacy met with key stakeholders from infectious disease, surgery, anesthesiology, and allergy for input and approval of all intervention material. These groups along with operative nursing received thorough education of the algorithm and intervention before implementation. From November 2018 to March 2019, a pharmacist performed BLA clarification telephone interviews. Patients were identified by screening for patients who met the inclusion criteria using the perioperative optimization clinic schedule. The telephone interview took place about 1 week

before the patient's clinic appointment to allow about 1 month to follow up with the allergy clinic, if recommended.

The interview reviewed the reaction, timing, and tolerance of other β -lactam antibiotics (Appendix A). On the basis of allergy history and the decision algorithm, first-line antibiotics, alternative antibiotics, or an electronic allergy testing referral was recommended and documented in the electronic medical record (EMR) (Figure 1). Antibiotic recommendations followed institutional guidelines, which are consistent with national surgical infection prophylaxis guidelines.³ Vancomycin was added to regimens if the patient had institution-specified methicillin-resistant *Staphylococcus aureus* (MRSA) risk factors.¹¹ The allergy label in the EMR was updated with details discussed during the interview (Appendix A). Patients referred to allergy testing followed up with one of the institution's allergy clinics to undergo a penicillin skin test and oral challenge with amoxicillin. BLA labels were removed if deemed appropriate by an allergist. The surgeon was notified of the intervention and recommendations via EMR documentation (Appendix B). The surgical team ordered preoperative antibiotics before the procedure. Patients who received the pharmacist intervention (PI) from November 2018 to March 2019 were compared to surgical patients meeting inclusion and exclusion criteria between November 2017 and March 2018 as a historical standard of care (SOC).

Endpoints. The primary endpoint was the use of β -lactams preoperatively. Secondary endpoints included clinical outcomes and process measures. Clinical outcomes included 30-day SSI and CDI, AKI, allergic reactions, and LOS. SSI was defined according to the Centers for Disease Control and Prevention definitions at day 30 after surgery.¹⁰ CDI was defined as presence of diarrhea and either a positive stool test result for the presence of *C. difficile* or its toxins or colonoscopic or histopathologic findings of pseudomembranous

colitis.¹³ Allergic reaction was defined as a type I hypersensitivity reaction, cytotoxic reaction, serum sickness, drug reaction with eosinophilia and systemic symptoms, severe cutaneous adverse reaction, or toxic epidermal necrolysis within 7 days of preoperative antibiotic administration. AKI was defined as an increase in serum creatinine levels of 0.3 mg/dL or serum creatinine levels greater than 1.5 times baseline within 4 days of preoperative antibiotic administration.¹⁴ LOS was defined as the time from the day of surgery to the day of discharge. Process outcomes included allergy labels updated or removed, recommendations accepted by the physician, vancomycin doses administered, and time to incision. Time to incision was defined as the time from operating room entry to the first incision.⁸ A nonequivalent dependent variable, sequential compression device order, was used to potentially control for maturation bias between the 2 study time periods.

Analysis. Continuous variables were compared using Mann-Whitney tests or *t* tests, as appropriate. Categorical data were compared using χ^2 tests. It was estimated that 46 individuals were needed per group for an effect size of 26% reduction in alternative antibiotics to meet 80% power and a 2-sided α value of 0.05.⁷ Data analysis was performed using SPSS, version 22.0 (IBM Corporation, Armonk, NY).

Results

Study population. Overall, 129 patients were screened for inclusion: 74 patients in the SOC group and 55 patients in the PI group. Fifty patients were included in the SOC group, and 37 patients were included in the PI group. The most common reason for exclusion in the SOC group and PI group was patients not having elective surgery ($n = 10$, 14%) and patients unable to be reached by telephone after 3 attempts ($n = 13$, 24%), respectively. Patient demographics and reported allergy characteristics are described in

Table 1. There were significantly more patients undergoing orthopedic surgery and neurosurgery in the PI group than in the SOC group. The SOC group had a greater variety of surgeries as compared to the PI group, including vascular, bariatric, and gynecologic surgeries. Allergy characteristics were similar between the groups. The most common reported allergen was penicillin (66% vs 61% in the SOC and PI groups, respectively). The most common patient-reported drug reactions were rash (34% vs 18%), unknown reaction (22% vs 21%), and multiple reactions (20% vs 21%) in the 2 groups.

Postintervention allergy outcomes and recommendations. All 37 patients in the PI group had allergy labels updated, and 23 of them (64%) were referred to an allergy clinic for testing. Of the patients who were referred, 13 (57%) followed up with an allergy clinic a median of 7 days (interquartile range [IQR], 4-9 days) after the telephone call. The allergy appointment occurred a median of 14 days (IQR, 13-16 days) before the day of surgery. Of these patients, 9 (69%) passed the penicillin allergy test, 3 (23%) failed testing, and 1 (8%) did not receive testing due to the patient's decision to defer allergy testing. Patients who passed the penicillin allergy test had the penicillin allergy label removed by an allergist. Of note, 2 patients had both a penicillin and cephalosporin allergy, so only the penicillin allergy label was removed after passing the allergy test while the cephalosporin allergy label remained on the chart.

Overall, the pharmacist recommendations for preoperative antibiotics were accepted by the surgeon for 28 (76%) of the 37 patients (Figure 2). The pharmacist recommended cefazolin in 19 (51%) patients. Seventeen of the 19 patients (89%) received cefazolin preoperatively. When alternative antibiotics were recommended, alternative antibiotics were given in 11 patients (61%) and cefazolin was given in 7 patients (39%) without any allergic reactions.

Preoperative antibiotics and outcomes. Cefazolin use significantly increased from 28% (14/50) to 65% (24/37) after the intervention ($P = 0.001$; Table 2). The most common preoperative regimen in the SOC group was clindamycin plus gentamicin (14/50). In the PI group, cefazolin (12/37) and cefazolin plus vancomycin (12/37) were used most commonly. Overall, vancomycin use increased from use in 19 patients (38%) to use in 22 patients (59%) ($P = 0.047$). Vancomycin monotherapy or vancomycin in combination with alternative antibiotics was used in 14 (28%) and 10 (27%) patients in the SOC and PI groups, respectively. Vancomycin was added to cefazolin due to presence of a MRSA risk factor in 5 (10%) and 12 (32%) patients in the SOC and PI groups. Overall, time to incision decreased by a median of 8 minutes ($P = 0.484$).

No SSIs occurred in the PI group. In the SOC group, 5 (10%) SSIs occurred ($P = 0.051$), and all were associated with alternative antibiotic use. AKI occurred in 2 (4%) patients who received alternative antibiotics preoperatively in the SOC group. No AKI occurred in the PI group. One instance of CDI occurred in a patient who received clindamycin plus gentamicin in the SOC group, while there was no incidence of CDI in the PI group. No allergic reactions occurred in either group. The LOS was a median of 2 days in each group with an IQR of 2.0 to 4.5 days and 2.0 to 2.0 days in the SOC and PI groups, respectively ($P = 0.014$). The nonequivalent dependent variable of sequential compression device order was similar between the groups (96% vs 97%, $P = 0.761$).

Discussion

BLA evaluation before surgery led to an increase in first-line β -lactam antibiotic use without negative safety outcomes. The harms of reported BLA have been well described in the literature and include increased odds of SSI, AKI, and CDI.^{3,4} Although this study had a smaller sample size, the study showed similar trends in higher SSI, AKI, and CDI with

alternative antibiotic use perioperatively. Notably, LOS was significantly different because there was a wider range of days of hospitalization in the SOC group than in the PI group. The success of the intervention relied on collaboration among the key stakeholders in the surgical process: pharmacy, infectious disease, surgery, and allergy leadership.

This study adds to the growing body of literature describing BLA clarification interventions in the preoperative setting. One of the challenges of BLA clarification is the lack of ownership of the allergy label. In previous literature, various disciplines have been described as taking responsibility for the BLA clarification process, including pharmacy, nurses, allergists, and infectious disease physicians.^{7,8} Pharmacists are well equipped to perform BLA clarification interviews and assess BLA in relation to cross-reactivity of β -lactams, severity of reaction, and prior antibiotic use. This study highlights the importance of the pharmacist's role in BLA clarification interviews and describes another service for pharmacy.

Although this study utilized a pharmacist to carry out the intervention, we recognize a potential role for pharmacy technicians and student pharmacists in this area. Previous studies successfully trained medication history pharmacy technicians and student pharmacists to conduct allergy histories.¹⁵⁻¹⁷ Similarly, with the proper training and pharmacist oversight, these pharmacy personnel could be trained to conduct telephone allergy history interviews. This possibility would allow both pharmacy technicians and student pharmacists to work at the top of their licensure and decrease the workload of pharmacists in a cost-effective manner. Additionally, this unique role could increase recruitment and retention of pharmacy technicians within health systems.

Various processes for allergy clarification in the perioperative setting have been described, including any combination of BLA interviews, penicillin skin testing, and oral challenge.^{7,8} Our intervention involves a process where all patients receive a BLA clarification telephone interview and the pharmacist then determines whether preoperative antibiotics can be recommended on the basis of the interview alone. If not, the pharmacist can refer the patient for a formal allergy evaluation before surgery, including a penicillin skin test and oral challenge, directly through the EMR. This allows a proportion of patients to avoid a separate visit to the allergy clinic if the interview alone can guide antibiotic prophylaxis.

We identified suboptimal patient follow-up with allergy clinics. One of the reasons for the lack of follow-up was not having an allergy clinic in the same location as the perioperative optimization clinic. Offsite allergy clinics introduced barriers such as transportation, inconvenience, and time. The results of this study were used to support the approval of a new allergy nurse practitioner position onsite. Part of the role of this new position is to sustain this BLA clarification intervention before surgery at patients' perioperative optimization clinic appointments and perform penicillin skin tests and/or oral challenge as indicated.

There are several limitations to the study. First, there was a limited time to follow-up of 30 days after surgery, so it is possible that some clinical outcomes were unaccounted for after the 30-day time point. Also, maturation bias, use of a historical control group, and lack of randomization are limitations inherent to a quasi-experimental study. To control for this, the study periods were chosen to correspond to the same time period during the year and a nonequivalent dependent variable (sequential compression device) was used to assess for prescribing practice changes for a similar quality measure, which nearly all patients

received. Hawthorne effect is possible because surgeons were aware of the intervention in action. Recall bias is another limitation because patients could have misremembered details of an allergy from the past. Additionally, there was a small sample size. However, our findings are consistent with past literature and are therefore likely not due to chance.

Conclusion

Clarifying reported BLA in the preoperative setting significantly increased use of first-line antibiotics for surgical infection prophylaxis. This intervention highlights an important role for pharmacists in optimizing services in the perioperative setting. Future exploration is needed to mitigate barriers to offering penicillin skin tests.

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Disclosures

Dr. Davis reports receiving honoraria for consulting from Allergan plc, Spero, and Tetrphase, unrelated to the submitted work. The authors have declared no potential conflicts of interest.

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References

1. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; Joint Council of Allergy, Asthma, and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105(4):259-273.
2. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14(1):73-156.
3. Blumenthal KG, Ryan EE, Li Y, et al. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66(3):329-336.
4. Vorobeichik L, Weber EA, Tarshis J. Misconceptions surrounding penicillin allergy: implications for anesthesiologists. *Anesth Analg*. 2018;127(3):642-649.
5. O'Brien WJ, Gupta K, Itani KMF. Association of postoperative infection with risk of long-term infection and mortality. *JAMA Surg*. 2020;155(1):61-68.
6. Cousin AS, Bouletreau P, Giai J, et al. Severity and long-term complications of surgical site infections after orthognathic surgery: a retrospective study. *Sci Rep*. 2020;10(1):12015.
7. Vaisman A, McCready J, Hicks S, Powis J. Optimizing preoperative prophylaxis in patients with reported β -lactam allergy: a novel extension of antimicrobial stewardship. *J Antimicrob Chemother*. 2017;72(9):2657-2660.
8. Moussa Y, Shuster J, Matte G, et al. De-labeling of β -lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis. *Surgery*. Published online May 8, 2018. doi:10.1016/j.surg.2018.03.004
9. Collins CD, Scheidel C, Anam K, et al. Impact of an antibiotic side chain-based cross-reactivity chart combined with enhanced allergy assessment processes for surgical

- prophylaxis antimicrobials in patients with β -lactam allergies. *Clin Infect Dis*. 2021;72(8):1404-1412.
10. McDanel DL, Azar AE, Dowden AM, et al. Screening for β -lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty*. 2017;32(9S):S101-S108.
11. Eriksson E, Hyder A, Kendall R, et al. *Henry Ford Health System Tier 1: Surgical Infection Prophylaxis in Adult Elective Surgery Policy*. Henry Ford Health System; 2019.
12. Centers for Disease Control and Prevention. *Surgical Site Infection Event (SSI)*. National Healthcare Safety Network; 2020.
<https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscscssicurrent.pdf>
13. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1-e48.
14. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-c184.
15. Krey SC, Waise J, Skrupky LP. Confronting the challenge of β -lactam allergies: a quasi-experimental study assessing impact of pharmacy-led interventions. *J Pharm Pract*. 2019;32(2):139-146.
16. Clark KE, Briand ME, Kapoor O, Pirasteh A. Impact of a standardized β -lactam allergy questionnaire on aztreonam use. *J Pharm Pract*. 2019;32(4):399-403.

17. Covington EW, Baldwin BJ, Warren E. Pharmacy-led β -lactam allergy interview (BLAI) reduces duration of fluoroquinolones within a community hospital. *Ann Pharmacother.* 2019;53(6):588-595.

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Figure 1. Reported β -lactam allergy clarification interview algorithm. An algorithm for the management of a surgical patient based on a comprehensive allergy history interview. BLA indicates β -lactam allergy; DRESS, drug reaction with eosinophilia and systemic symptoms; IgE, immunoglobulin E; SCAR, severe cutaneous adverse reaction.

Figure 2. Pharmacist intervention group antibiotic recommendations. Shown are pharmacist recommendations for preoperative antibiotics and the antibiotic administered.

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Table 1. Patient Demographics and Reported Allergy Characteristics

Characteristic	SOC (n = 50)	PI (n = 37)
Age, median (IQR), years	69 (61-76)	66 (61-73)
Male sex, No. (%)	17 (34)	12 (32)
Caucasian race, No. (%)	33 (67)	19 (51)
Operation type, No. (%)		
Orthopedic	19 (38)	22 (60)
Neurosurgery	6 (12)	12 (32)
Urological	4 (8)	1 (3)
Cardiac	1 (2)	2 (5)
Other	20 (40)	0
ASA classification, median (IQR)	3 (3-3)	3 (3-3)
Body mass index, median (IQR)	30 (29-36)	29 (25-34)
Sequential compression device order, No. (%)	48 (96)	36 (97)
Reported allergy drug, No. (%)		
Penicillin	33 (66)	23 (61)
Multiple β -lactam antibiotics	7 (14)	4 (12)
First-generation cephalosporin	6 (12)	2 (6)
Other penicillin	3 (6)	8 (21)
Carbapenem	1 (2)	0
Reported drug reaction, No. (%)		
Rash	12 (24)	7 (18)
Unknown	11 (22)	8 (21)
Multiple reactions	10 (20)	8 (21)
Hives	3 (6)	6 (15)
Anaphylaxis	5 (10)	2 (6)
Swelling	3 (6)	1 (3)
Gastrointestinal intolerance	4 (8)	2 (6)
Other	2 (4)	3 (9)

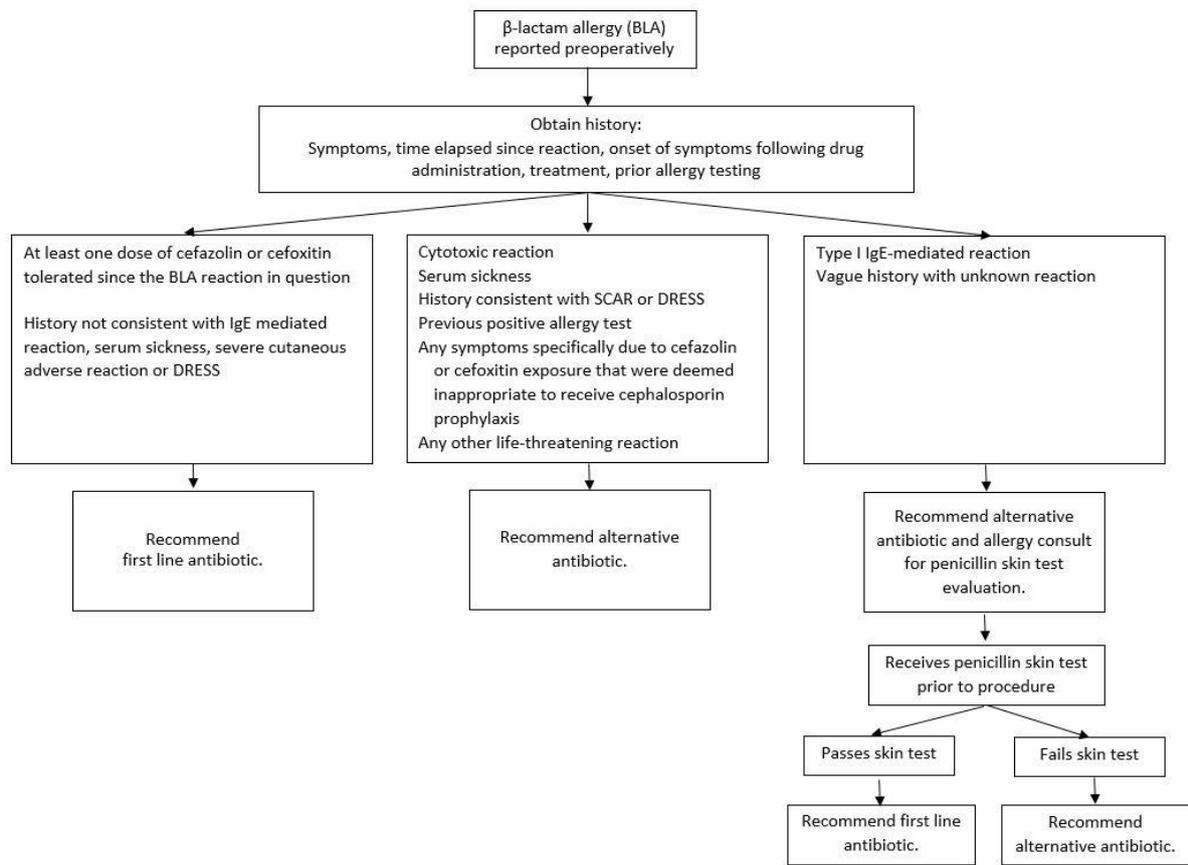
Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range; PI, pharmacist intervention; SOC, standard of care.

Table 2. Preoperative Antibiotic Management and Safety Outcomes

Treatment or Outcome	SOC (n = 50)	PI (n = 37)	P Value
β-lactam antibiotic administered, No. (%)	14 (28)	24 (65)	0.001
Vancomycin administered, No. (%)	19 (38)	22 (59)	0.047
Surgical site infection, No. (%)	5 (10)	0	0.051
<i>Clostridioides difficile</i> infection, No. (%)	1 (2)	0	0.387
Allergic reaction, No. (%)	0	0	–
Acute kidney injury, No. (%)	2 (4)	0	0.746
Length of hospitalization, median (IQR), days	2 (2-4.5)	2 (2-2)	0.014

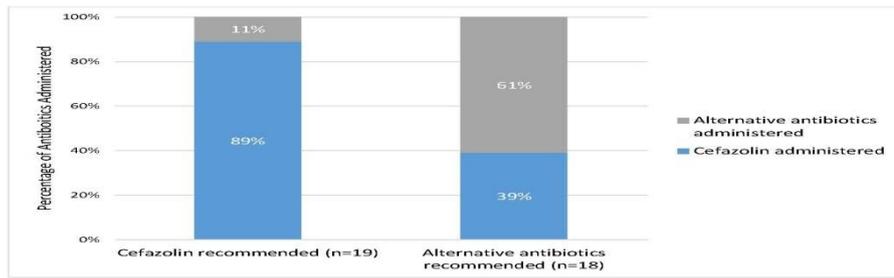
Abbreviations: IQR, interquartile range; PI, pharmacist intervention; SOC, standard of care.

Figure 1



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Figure 2



	Cefazolin administered	Alternative antibiotics administered
Cefazolin recommended (n=19)	89%	11%
Alternative antibiotics recommended (n=18)	39%	61%